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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,993	09/07/2006	Satoshi Kanazawa	80186(302730)	6413

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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/591,993	KANAZAWA ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 11 September 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.

   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,2 and 5*.
   Claim(s) withdrawn from consideration: *11-17*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____

13. ☐ Other: _____.

/Q. JANICE LI/
Primary Examiner, Art Unit 1633

Continuation of 11. does NOT place the application in condition for allowance because:

35 USC 103 - Harton, Lindqvist and Otten

Claims 1, 2 and 5 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Harton et al. (Molecular and Cellular Biology, Sept. 2000; 20(17):6185-6194) in view of Lindqvist et al. (Trends in Genetics. 2002; S7-S13) and further in view of Otten et al. (Journal of Immunology. 2003; 170: 1150-1157) for the reasons of record and the comments below.

The applicant's arguments and claim amendments have been fully considered but are unpersuasive. The applicant has amended claim 1, but has not substantially changed the scope of the instant claims.

The applicant has argued that the cited references do not teach "administration of at least two low doses…of type II collagen to a mouse or rat resulting in a human rhematoid arthritis phenotype in the mouse or rat." The examiner finds this argument unpersuasive, because the claimed invention is a product (i.e., a transgenic mouse or rat comprising a heterologous collagen II promoter and MHC II transactivator gene). The cited art teaches these limitations. The instant claims to a transgenic mouse or rat also contain limitations wherein administration of type II collagen to the transgenic animal induces pathologic conditions of human rheumatoid arthritis. The obviousness rejection has indicated that the transgenic mouse or rat of Harton, Lindqvist and Otten displays pathologic conditions of human rheumatoid arthritis when administered type II collagen.

Harton teaches that increased expression of MHC class II transactivator induces pathological symptoms of Rheumatoid Arthritis. Otten teach a transgenic mouse expressing CIITA in all organs and further suggest this mouse is a model for RA. Lindqvist teach a transgenic mouse having cartilage-restricted expression based on a type II collage promoter. In addition, the cited art teaches criteria for classification and characterization of rheumatoid arthritis in mouse models of RA, such as those listed in claim 5. The important requirement for induction of RA symptoms in a transgenic mouse comprising CIITA gene seems to be expression of CIITA. Without evidence to the contrary, a skilled artisan would conclude the type II collage promoter to be sufficient to produce enough CIITA to generate RA symptoms.

The applicant has summarized his argument as, "none of the cited references teaches a transgenic mouse, which when administered at least two low doses (0.01 mg to 0.05 mg) of type II collagen results develops (sic) a human rheumatoid arthritis phenotype." Based on the evidence of record, the examiner accepts that it is possible to induce symptoms of arthritis with the relatively low doses of collagen as in the instant claim. However, because the structure of the claimed mouse is suggested by the cited art and the applicant has not indicated how the claimed mouse has advanced scientific knowledge or what is the inventive feature of inducing Rheumatoid Arthritis symptoms in a mouse, using only a low dose of collagen, the examiner is not persuaded by the applicant's argument regarding the low dose aministration of type II collage as a secondary consideration. After all, the use of the collage type II promoter was suggested in other mouse models of RA and transgenic mice overexpressing CIITA were generated by other groups and suggested as a model of RA.

The applicant has also argued that there is no motivation to combine the cited references. The examiner suggests that in light of the recent KSR decision, this necessity for a "reason or suggestion" is no longer required. KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision Ex parte Smith, --USPQ2d, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396). The examiner has provided a rationale for combining the cited art (see rejection reiterated below). The structure of the claimed transgenic mouse/rat is suggested by the prior art. Induction of human RA symptoms in such models by administering type II collagen is suggested by the cited art. Each of the elements (transgenic mice comprising CIITA; nexus between CIITA expression and RA; animal models of RA which include administration of collagen II; and suggestions for joint-specific (collagen) expression of genes in animal models of RA) are taught by Harton or Lindqvist or Otten and further they are taught in various combinations and are shown to be used in mouse models of rheumatoid arthritis. It would be therefore predictably obvious to use a combination of these elements in a mouse models of rheumatoid arthritis.

The applicant further argues the cited references fail to provide a reasonable expectation of success "in arriving at Applicant's claimed invention." Contrary to the applicant's arguments, the claimed invention is suggested by the cited art.. The structure of the claimed transgenic mouse/rat is suggested by the cited art. The induction of symptoms of human Rheumatoid Arthritis in such transgenic animals following administration of type II collagen is also suggested by the cited art. The skilled artisan would have had a reasonable expectation of success in combining the teachings of Harton et al. and Lindqvist et al. and Otten because making transgenic mice having tissue-specific expression patterns was known in the art at the time of the instant invention.

Taken as a whole, the examiner is not persuaded by the applicant's arguments regarding the secondary considerations (i.e., unexpected nature of a transgenic mouse wherein induction of RA symptoms in said transgenic mouse, using only a low dose of collagen,) is insufficient to demonstrate the instant invention non-obvious.

Therefore, the examiner hereby maintains the rejection of claims 1, 2 and 5 under 35 U.S.C. 103(a) as being obvious over Harton et al. in view of Lindqvist et al. and further in view of Otten.

The examiner reiterates the pending rejection:

Claims 1, 2 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harton et al. (Molecular and Cellular Biology, Sept. 2000; 20(17):6185-6194) in view of Lindqvist et al. (Trends in Genetics. 2002; S7-S13) and further in view of Otten et al. (Journal of Immunology. 2003; 170:

1150-1157).

Claim 1 is directed to a transgenic mouse or rat comprising a foreign DNA, the foreign DNA comprising a type II collagen promoter and a DNA selected from the group consisting of MHC class II transactivator gene, an active region of the MHC class II transactivator gene, and a mutant MCH class II transactivator gene, said mutant having a master switch function for controlling expression of the MHC class II genes, wherein said DNA is located under control of said type II collagen promoter, wherein administration of type II collagen to said transgenic mouse or rat at a dose of 0.01 mg to 0.05 mg two or more times results in presentation of pathologic conditions of human rheumatoid arthritis in said transgenic mouse or rat.

Harton et al. teach class II MHC is involved in rheumatoid arthritis (page 6185, col.1, Introduction, lines 9-11) and CIITA expression is required for expression of class II MHC (page 6185, col.2, Introduction, lines 10-12). Harton et al. demonstrate the nexus between class II transactivator (CIITA) expression for the expression of class II MHC and its role with MHC in rheumatoid arthritis. Further, Harton suggests that enhancement of class II MHC through CIITA is involved in critical events of pathogenesis and autoimmune diseases such as RA (page 6191, col.1, last parag.).

Harton et al. does not teach a transgenic non-human mammal comprising CIITA operably linked to collage II promoter.

Lindqvist et al. teach a variety of mouse models of rheumatoid arthritis. In particular, Lindqvist et al. teach collagen induced arthritis (CIA), in which mice display symptoms similar to human rheumatoid arthritis when injected with type II collagen. Lindqvist et al. also teach transgenic models of RA where the effect of a specific gene is evaluated for its involvement in the arthritis development (page S8, col.2). Lindqvist et al. teaches "RA is genetically associated with the major histocompatibility complex (MHC) class II" (page S8, col.1, parag.1). Lindqvist et al. teach a transgenic mouse having cartilage-restricted expression based on a type II collage promoter (page S9, col.2 and Fig.1).

Lindqvist et al. does not teach a transgenic non-human mammal comprising CIITA operably linked to collage II promoter, but does suggest other transgenic animal models for RA, including some which have collagen-specific expression. Lindqvist et al. further teaches induction of RA symptoms in the CIA model by administration of collagen. Lindqvist et al. also suggests making generic mouse models of RA by expression of "a specific gene." Finally, Lindqvist et al. teach the connection between MHC II expression and rheumatoid arthritis. Additionally, Lindqvist et al. teaches symptoms in mouse models of RA which correspond to claim 5 (Table 1); the list in claim 5 is commonly used to identify pathological conditions found in mouse models of RA and is therefore obvious.

Otten et al. teach "Increased CIITA and MHC-II expression…occur in autoimmune conditions such as rheumatoid arthritis" (page 1150, col.2, last parag.). Otten et al. also teach a transgenic mouse expressing CIITA in all organs (page 1153, col.1, parag.1). Otten et al. teach "[i]n our transgenic mouse, the CIITA transgene induces MHC-II expression in most cell types" (page 1156, col.2, CIITA transgenic mice section).

While Otten et al. emphasize the affect of CIITA overexpression on immune cell function, it is clear that their transgenic CIITA mouse is suggested as being a model of rheumatoid arthritis. However, Otten et al. do not teach a transgenic non-human mammal comprising CIITA operably linked to collage II promoter.

However, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to make a transgenic non-human mammal comprising a foreign DNA, the foreign DNA having a DNA which is a MHC class II transactivator (CIITA) gene, and which is under the control of a type II collagen promoter.

The person of ordinary skill in the art would have been motivated to make a transgenic mouse comprising a MHC class II transactivator (CIITA) gene which is under the control of a type II collagen promoter. Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (transgenic mice comprising CIITA; nexus between CIITA expression and RA; animal models of RA which include administration of collagen II; and suggestions for joint-specific (collagen) expression of genes in animal models of RA) are taught by Harton or Lindqvist or Otten and further they are taught in various combinations and are shown to be used in mouse models of rheumatoid arthritis. It would be therefore predictably obvious to use a combination of these elements in a mouse models of rheumatoid arthritis.

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Harton et al. and Lindqvist et al. and Otten because making transgenic mice having tissue-specific expression patterns was known in the art at the time of the instant invention.

Therefore the transgenic non-human mouse as taught by Harton et al. in view of Lindqvist et al. and further in view of Otten et al. would have been prima facie obvious over the transgenic mouse having a phenotype of rheumatoid arthritis-like symptoms of the instant application.

The exmainer finds the applicant's arguments unpersuasive. Accordingly, the pending claims remain rejected for the reasons of record.

/SDL/ Scott Long, patent examiner, art unit 1633